HYPERSENSITIVITY REACTIONS TO THE PRIMARY ANTITUBERCULOUS DRUGS IN SINGAPORE*

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INTRODUCTION

Drug intolerance, including hypersensitivity reaction to the three primary antituberculous drugs i.e. Streptomycin, (SM), Para-aminosalicylate, (PAS) and Isoniazid, (INH) is well known and is one of the important causes of failure of treatment. These drugs have been in use for the past two decades. However, no reported study has been made of hypersensitivity reactions to these drugs in Singapore. Most reports in the literature have been retrospective studies. One of the few prospective studies is that of Smith and Zirk[8] from Birmingham, England. They included toxic reactions in their study. Toxic reactions are organ specific, like deafness and vertigo due to streptomycin, are dose dependent and require stoppage or reduction of the dosage of the drug. Side-effects like the gastrointestinal upsets due to PAS are usually mild and do not warrant stoppage and usually subside with symptomatic treatment or a change of the form of the drug. Hypersensitivity reactions on the other hand are usually not dose dependent, are reproduceable with even a small dose, and the offending drug or drugs can usually be continued in most cases after appropriate desensitisation.

We report here a prospective study of the incidence and types of hypersensitivity reactions to the three primary antituberculous drugs in patients undergoing treatment in Unit III, Tan Tock Seng Hospital.

MATERIAL AND METHODS

All new cases above 10 years registered into the Unit from 1st January 1969 to 31st December 1969 for treatment were admitted into the study. In all there were 660 cases and these represented a random sample as every fourth new case on treatment was registered into the Unit (there being four units in the hospital). The study was stopped at the end of June 1970 as in our experience, it was unlikely that hypersensitivity reactions will occur after a period of six months of chemotherapy. Of the 660 cases, all but 31 had standard triple chemotherapy for at least 3 to 5 months initially, followed by PAS/INH in tablet form, for a complete course of two years. All cases were given INH, 652 had PAS and 627 had streptomycin. Streptomycin was given in a dose of 1 gm. or ¾ gm. daily according to the age and weight of the patient. The standard dose for PAS was 10 gms. Sodium PAS and for INH 300 mg. daily.

Reactions were allowed to completely subside by stoppage of chemotherapy. Test doses were then given to determine the offending drug or drugs.

RESULTS

Incidence

Of the 660 cases, 468 were males and 192 were females. There were 62 with hypersensitivity reactions and of these, 32 were males and 30 were females (Table I). The incidence of hypersensitivity reaction for the whole series was 9·4%. The incidence for females was 15·6% and that for males was 6·8% (Table I). This difference is highly significant with a p value of $<0{\cdot}001$.

TABLE I

INCIDENCE OF HYPERSENSITIVITY REACTION

	Total	Male	Female
No. on treatment	660	468	192
No. with reaction	62	32	30
% with reaction	9·4	6·8	15·6

The number with reaction to one drug only was 39, to two drugs was 18 and to all three drugs was 3. The relative percentages are given in Table II. There were two cases where no challenge dose was given. One had severe exfoliative

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TABLE II

REACTION TO ONE OR MORE DRUGS

	No.	% of Total Pts.
Reaction to one drug	39	5·9
Reaction to two drugs	18	2·8
Reaction to three drugs	3	0·4
Not challenged	2	0·3

TABLE III

INCIDENCE TO INDIVIDUAL DRUG

	SM	PAS	INH
No. with reaction	30	45	6
No. at risk	627	652	660
Percentage	4·8	6·9	0·9

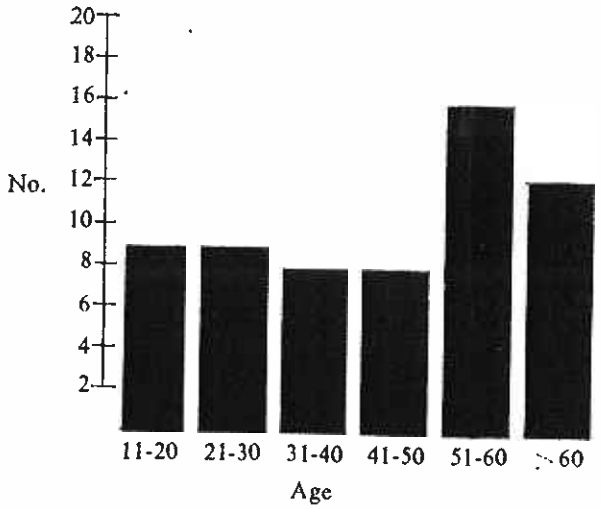

Fig. 1. Age incidence.

TABLE IV(a)

INCIDENCE OF REACTIONS IN VARIOUS ETHNIC GROUPS

	No. of Patients	No. with Reactions	% with Reactions
Chinese	564	50	8·9
Malays	58	9	15·5
Indians/ Pakistanis	36	2	5·5
Others	2	1	50·0
TOTAL	660	62	—

TABLE IV(b)

DISTRIBUTION OF ETHNIC GROUPS

	No.	%
Chinese	564	85·4
Malays	58	8·8
Indians/Pakistanis	36	5·4
Others	2	0·4
TOTAL	660	100·0

TABLE IV(c)

PATIENTS WITH REACTIONS—ETHNIC DISTRIBUTION

	No.	%
Chinese	50	81·0
Malays	9	14·0
Indians/Pakistanis	2	3·3
Others	1	1·7
TOTAL	62	100·0

dermatitis and jaundice and died 27 days later. The other died before any challenge dose could be given. Both showed extensive liver necrosis at necropsy.

Those with double drug reaction were mostly due to SM and PAS in those who had these two drugs in the regime for the initial 3 to 5 months.

Incidence for Individual Drugs

The incidence of hypersensitivity reactions in relation to the number of patients at risk to each individual drug is given in Table III. Of the 6 cases due to INH, 2 were doubtful but have been included. In these two instances, INH was challenged a little too soon and it was possible that the residual effect of the original reaction had not completely subsided. If these two cases were excluded, then the incidence due to INH would be only 0·6%.

Sex and Age Incidence

From Table I, it can be seen that reactions in female patients were more than twice as frequent as in males.

The age distribution of patients of both sexes were about the same. Reactions occurred most frequently in those 50 years of age and over (Fig. 1).

Relationship to Ethnic Groups

The incidence of reactions in relation to ethnic groups is given in Table IV(a).

It was highest in the Malays, being 15·5% compared with 8·9% in the Chinese. Table IV(b) shows the population and ethnic distribution of the group. 85·4% were Chinese and 8·8% only were Malays.

But of those 62 patients with reactions, Malays constitute 14% (Table IV(c) whereas the percentages for the other ethnic groups remained in the same ratio as for the population studied [Table IV(b)]. However, when compared statistically with the Chinese, the higher incidence in the Malays was not very significant, the p value being between 0·2 and 0·3.

Time of Occurrence of Reaction

The time intervals after initiation of treatment and the occurrence of hypersensitivity reactions are shown in Table V.

Reactions occur as early as the first week and one case occurred at the 6th month. The commonest period was during the second and third weeks (61·3%). Between the fourth and eighth week, there was an even distribution. There were 7 cases occurring in the 3rd month. Reaction occurring from the 4th month onwards were uncommon.

TABLE V

TIME OF OCCURRENCE OF REACTION

Week	1st	2nd	3rd	4th	5th	6th	7th	8th
No. of pts.	1	23	15	3	1	3	4	2

Month	3rd	4th	5th	6th	7-12th	>12th
No. of pts.	7	1	1	1	0	0

Types of Reaction

By far the commonest manifestation of allergy was fever with skin eruptions which range from simple erythema to severe exfoliative dermatitis Maculo-papular rash was the commonest skin manifestation. Twenty-nine patients had a combination of fever and rash. Rash alone occurred in 18 cases. This was often associated with pruritus. Exposure to light seemed to precipitate or aggravate the rashes. Fever without rash occurred in 13 cases. The fever quite often came on suddenly and might rise to 103°F or 104°F. It usually occurred within half an hour to 3 to 4 hours following injection or ingestion of the drug. If the drugs were taken off, the temperature returned to normal dramatically. The next commonest reaction was suffusion of the conjunctiva with tearing which occurred in 12 patients. Myalgia occurred in nine patients. Seven developed lymphadenopathy. These usually involved the cervical and sometimes the axillary nodes and subsided spontaneously when the allergic phenomenon improved. The lymph nodes were usually rubbery in consistency. Kalinowski *et al*[6] reported only one instance in their series of 3,148 patients studied and Cannemeyer *et al*[3] reported 14 of 5,000 patients taking PAS. Hepatomegaly occurred in 5 patients, all without jaundice and one case had splenomegaly with enlargement of the liver as well. Arthralgia occurred in 2 patients. Two of the 62 cases showed roentgenogram changes. One patient who died showed increased interstitial lung markings generally and the other patient showed increased haziness in the left lower zone associated with a small left pleural effusion. This patient had steroids and the effusion and haziness cleared up fairly rapidly. There was no associated eosinophilia in these two patients, as was the three reported by Jackson[5] though Kalinowski *et al*[6] reported three and Holmboe[4] found ten in the literature and added one of his own in which there was associated eosinophilia. Their cases were due to PAS. One of our cases was hypersensitive to INH. The one who died was not challenged because of severe reactions.

The frequency of occurrence of the above reactions is given in Table VI. In some cases, more than one manifestation occurred in the same patient.

TABLE VI

TYPES AND FREQUENCY OF ALLERGIC MANIFESTATION

Manifestation	No.	%
Fever with rash	29	46·7
Rash alone	18	29·0
Fever alone	13	21·0
Suffused eyes	12	19·4
Myalgia	9	14·5
Lymphadenopathy	7	11·3
Hepatomegaly	5	8·0
Arthralgia	2	3·2
X-ray changes	2	3·2
Splenomegaly	1	1·6

Associated Laboratory Findings

Eosinophilia occurred in 46% of the 52 cases where this test was done. The commonest range was 5-8%. The lowest was 4% and the highest was 15%. A raised eosinophil count may be helpful in substantiating a diagnosis of drug hypersensitivity but need not be raised to make a diagnosis. The total white count was non-specific.

Raised serum glutamo-pyruvic transaminase occurred in 32% of 56 cases. The majority had no jaundice with the exception of the two who died. The presence of severe jaundice is a bad prognostic sign in the presence of severe hypersensitivity reaction like exfoliative dermatitis. The laboratory findings are given in Table VII.

TABLE VII

LABORATORY FINDINGS

	Raised	No. Test Done	%
Eosinophia	24	52	46
S.G.P.T.	18	56	32

DISCUSSION

This study of 660 patients includes only the hypersensitivity reaction due to the three primary antituberculous drugs. The largest prospective study previously reported is that of Smith and Zirk[8] who reported on 628 cases. Retrospective studies like those of Kalinowski *et al*[6] and Berte *et al*[1] have included larger number of patients.

In our study, the total incidence of allergic reactions as well as that to individual drugs were almost the same as those of Kalinowski *et al*[6] with the exception to INH in which we had a slightly higher incidence (Kalinowski: total incidence 9·8%; SM 5·8%; PAS 7·2%; INH 0·1%; the present study: 9·4%; 4·8%; 6·9%; 0·9% respectively). However, 2 cases due to INH in our study were doubtful but have been included. Berte *et al*[1] gave the incidence of intolerance to INH as 1·3% but they included toxic reactions like peripheral neuropathy which occurred in 3 of their 22 patients. Smith and Zirk[8] reported 8% for SM, 8·7% for PAS and 12% for their total incidence. There was no reaction due to INH.

Hypersensitivity reaction to both SM and PAS occurred in 2·8% of our patients but in 5% of that of Smith and Zirk[8]. Mcleod[7] gave an incidence of 8% in 144 patients on SM an PAS. The British Medical Research Council[2] reported an incidence of 4% in 115 patients treated with SM and PAS.

Most of the hypersensitivity reactions recorded in our study were the same as those reported by other authors, the commonest being fever with rash. The manifestation is easily recognisable as the fever subsides dramatically when the drug or drugs are withdrawn. We have not encountered any case of asthma. There were only 2 cases with pulmonary changes. There were 2 cases with arthralgia and this manifestation was mentioned only by Berte *et al*[1] who had 3 such cases.

As in most studies, females were more susceptible, the incidence being twice as common as in males. In both the females and males, there was a slightly higher incidence of reactions in those above 50 years. This was not the finding of Smith and Zirk[8] who reported no increase in allergic reactions with age.

The commonest period for the occurrence of drug hypersensitivity was in the second and third weeks and this finding agreed with most others. Smith and Zirk[8] recorded the second to the fifth week as the most susceptible period. Reactions occurring from the fourth month onwards were uncommon.

SUMMARY

A prospective study of hypersensitivity reactions in 660 new cases above 10 years of age treated with the three primary antituberculous drugs is reported.

The overall incidence was 9·4%. Females were more susceptible, the incidence being 15·6% as against 6·8% in males. 5·9% of the 62 cases were due to one drug only, 2·8% to 2 drugs and 0·4% to all 3 drugs.

In terms of individual drugs, 4·8% developed allergic reactions to SM, 6·9% to PAS and 0·9% to INH. However, if two doubtful cases were excluded for INH, then the incidence was only 0·6%.

The highest incidence of reactions (61·3%) occurred during the 2nd and 3rd weeks. Fever with rash was the commonest manifestation, occurring in 46·7% of the 62 cases. Suffused eyes and tearing occurred in 19·4%, myalgia in 14·5% and lymphadenopathy in 11·3%. Some of these manifestations occurred in the same patient.

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